REMARKS

Applicants respectfully request reconsideration. Claims 1-5 were previously pending in this application. By this amendment, Applicants are amending claims 1 and 2. Claim 1 has been amended to clarify that the method steps include comparison of a control (normal) coding region/gene in an 8.9 cM region of human chromosome 18q disposed between polymorphic markers D18S68 and D18S979 or a fragment thereof that is compared to the coding region/gene in the DNA from a person afflicted with a bipolar disorder. Support for the amendment can be found in the specification as filed at least at page 10, lines 32-35, and page 20, lines 17-27. With respect to the use of the term "equivalent" region, Applicants have amended claims 1 and 2 to clarify that the claimed methods include comparison of a coding region in the DNA of an individual afflicted with bipolar disorder in a plurality of control individuals, which may include DNA from normal healthy individuals (see page 10, lines 25-35; page 10, lines 23-27) or the DNA in a YAC clone. In addition, claims 1 and 2 have been amended to remove the term "equivalent region".

Claims 1-5 are pending for examination with claims 1 and 2 being independent claims. No new matter has been added.

Rejections under 35 U.S.C. §112

The Examiner rejected claims 1-5 under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement.

Applicants have amended claims 1 and 2 and submit that claims 1-5 are fully enabled by the application as filed. Applicants respectfully submit that the specification as filed contained sufficient guidance to enable one skilled in the art to identify coding regions within the region of chromosome 18 delineated by markers D18S68 and D18S979, or between polymorphic markers D18S60 and D18S61 of the YAC clone as provided, through the application of routine procedures, without undue burden.

Applicants have amended claims 1 and 2 to remove language relating to "equivalent regions". Applicants submit that the claimed methods include a comparison of a coding region of DNA from an individual afflicted with bipolar disorder with DNA of the coding region from a

plurality of control individuals or the DNA in a YAC clone, and that from such comparison, one of skill in the art can identify at least one coding region/gene or mutated or polymorphic variant thereof as associated with bipolar disorder. The DNA comparison requires only standard methods known to those of skill in the art, now that Applicants have identified and disclosed the specific region for comparison.

With respect to the breadth of the claims, at page 3 of the Office Action, the Examiner states that the claims are broadly written and refers to the claims as reciting methods of identifying regions/genes in "any mood disorder". Applicants respectfully submit that the claims are not drawn to identifying a region of DNA associated with "any mood disorder" but rather are drawn to methods with which to identify a region of DNA associated with bipolar disorder, which is a disorder that is much more limited in scope than the range of disorders considered by the Examiner in rejecting the claims.

With respect to predictability or unpredictability of the art and degree of experimentation, the Examiner states at page 5 of the Office Action that "(T)he specification does not disclose a single gene or coding region within the region of D18S68-D18S979. Further, the specification does not disclose any particular mutations or polymorphisms within the region of D18S68-D18S979 which are associated with BP II". Applicants respectfully submit that this is not the claimed invention. Applicants do not claim specific genes or coding region within the region of D18S68-D18S979, but rather claims a method with which such genes or coding regions can be identified. The invention is based, in part, on Applicants' identification of the D18S68-D18S979 region of chromosome 18 as containing a gene or coding region that is associated with bipolar disorder. Applicants identified this region through linkage analysis and Applicants' discovery permits one of ordinary skill in the art to use the newly identified region for the identification of a human coding region/gene including mutated or polymorphic variants thereof that is associated with bipolar disorder. Although the distinction between the Examiner's interpretation of the claims and the actual subject matter claimed may appear subtle, it is key to understanding the scope of the invention. Applicants are not claiming to have identified specific genes or coding regions, but based on discovering that a region of DNA is associated with bipolar disorder, are claiming methods to identify such one or more coding regions or genes associated with bipolar disorder.

The Examiner states at page 5, second full paragraph, that "(O)nce a region associated with a gene is known, extensive experimentation remains to determine which, if any genes within this region are sufficiently linked to a disease in order to allow for diagnosis of the disease by detecting the gene". Applicants submit that the claimed methods involve the identification of a gene or region associated with bipolar disorder and that the steps needed to use the information provided by Applicants to identify a specific gene or coding region or variant thereof, would be routine to one of ordinary skill in the art. Applicants submit that experimentation required to practice the claimed invention, does not constitute undue experimentation. Applicants submit that those of ordinary skill in the art would recognize that all of the steps and experiments necessary to identify a gene in the D18S68-D18S979 region, a region disclosed for the first time by Applicants, are routine. Applicants submit that a technician of ordinary skill in molecular biology would be able to carry out the claimed methods for the identification of a gene or variant that is associated with bipolar disorder now that Applicants have provided the limited region in which to apply these routine methods.

In contrast to the Examiner's assertion at the bottom of page 5, that "the specification outlines the methodology by which a research could perform extensive, trial-by-error experiment in order to try to identify genes/coding regions", the specification provides a clear list of steps and procedures that are well known and routinely used in the art. Applicants submit that a person of ordinary skill in the art would readily select and implement routine methods in conjunction with the teaching in the specification to practice the claimed invention. The steps and methods outlined in the specification, and reiterated by the Examiner at page 6 of the Office Action, may be time-intensive and labor-intensive, but that does not mean they are random, trial-and-error methods, but rather are representative of standard, routine, everyday practice for those of ordinary skill in the art.

With respect to the amount of guidance presented in the specification as filed, the Examiner recognizes at page 9 of the Office Action that "methods for performing linkage analysis and for sequencing genes and comparing the sequence of genes from patients and control individuals are known in the art" but states that "such methods provide only the general guidelines that allow researchers to search for novel genes and mutations." Applicants submit that the identification of the D18S68-D18S979 region through the use of linkage analysis

provides sufficient guidance for one of ordinary skill in the art to use methods described in the specification, which the Examiner acknowledges are art-known methods, to identify a gene or coding region associated with bipolar disorder. The Examiner states, also at page 9 of the Office Action, that "the mere presence of a genetic variation between the DNA of one affected person and the DNA of one control person does not alone indicate that the variation is associated with a disorder." Applicants have amended claim 1 to indicate that the DNA of a person afflicted with bipolar disorder can be compared to the DNA of one or more control individuals. Applicants submit that comparing DNA in the region of D18S68-D18S979 of a person afflicted with bipolar disorder with control in the region of D18S68-D18S979 of a plurality of control individuals not afflicted with bipolar disorder allows one of skill in the art to identify a coding region/gene that is associated with bipolar disorder. Thus, using methods of the invention, DNA from control individuals can be compared to DNA of individuals afflicted with bipolar disorder to determine coding regions/genes and polymorphisms and mutations that are associated with bipolar disorder. Applicants concur with the Examiner's statement at page 13, that not all polymorphisms present between D18S68-D18S979 will necessarily be linked to bipolar disorder, but successful use of the invention does not require that each polymorphism be so linked. Routine practices in molecular biology will readily allow one of ordinary skill in the art to do the analysis necessary to determine whether a polymorphism in the D18S68-D18S979 region is indeed associated with bipolar disorder.

The support of the rejection, the Examiner quotes the Court in *Genetech Inc. v. Novo* Nordisk 42 USPQ2d 1001 as holding that "(I)t is the specification, not the knowledge of one skill in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". Applicants submit that a novel aspect of the invention is Applicants' determination, using linkage analysis, of the region of D18S68-D18S979 and that this novel aspect of the invention can be used by those of ordinary skill in the art in conjunction with known, routine practices to identify coding regions/genes that are associated with bipolar disorder. The Examiner also states that "the disclosure of a 8.9cM region linked to BPII is not equivalent to teaching specific sequences that constitute coding regions/genes or mutations that as associated with a BP disorder." Applicants agree with this characterization by the Examiner but assert that because the claimed invention is not the specific sequences that constitute coding

regions/genes or mutations associated with bipolar disorder, Applicants are not required to teach specific sequences that constitute coding regions/genes or mutations. Applicants provide the chromosomal location and tools to allow one of skill in the art to identify a gene, coding region, mutation or polymorphism associated with bipolar disorder. Applicants' discovery narrowed the candidate region on chromosome 18 to a region sufficiently small that they were able to provide a contig map of publicly available YAC clones containing the actual DNA of the region between markers D18S60 and D18S61, including the candidate region between markers D18S68 and D18S979. The availability of this contig map and the DNA present in the YAC clones further facilitates the identification of candidate coding regions using the claimed methods.

With respect to LOD scores, and the significance of linkage in family MAD31, Applicants submit that one of ordinary skill in the art would recognize the results set forth by Applicants in the application as evidence of linkage. As discussed in the responses previously filed, Applicants did not carry out a full genome scan, but rather a multipoint linkage analysis using STR markers from a particular region of chromosome 18. Therefore the threshold for significant linkage is not a LOD score of 3.0 as would be appropriate for a genome-wide scan, but is a value of 2.0. The Declaration of Christine Van Broeckhoven filed with the last response indicates "the LOD score of +2.0 was indicative of significant linkage in this study, taking in to account the design of the particular study carried out in family MAD31". At page 14 of the Office Action mailed January 5, 2006, the Examiner responds to the Declaration by stating that the Lander publication suggests that for a lower LOD score to be indicative of significance linkage, it should be in the context of a replication study. The Examiner then concludes that "(T)he results set forth in the present application do not appear to constitute a replication study." Applicants submit that as indicated in the specification as filed at page 3, lines 31-33, the linkage results obtained by Applicants were the result of a replication study to test linkage with chromosome 18. Thus, the Lander reference provides no basis for the Examiner's rejection of the significance of the linkage results set forth in the specification as filed.

Applicants submit that the linkage results provided in the application as filed and that the results presented in the application as filed would be accepted as evidence of significant linkage by one skilled in the art in the type of study carried out by Applicants. Because the specification demonstrates a significant genetic linkage between the relevant region of human chromosome 18

and bipolar disorder, Applicants submit that there would be a high expectation of success that an analysis of the region of chromosome identified by Applicants, would lead to the identification of one or more polymorphisms and genes associated with susceptibility to disease. Now that Applicants have shown a very specific region of the genome to be associated with bipolar disorder, one of skill in the art could use that information to search for, and indeed would expect to find, polymorphic alleles and genes that are associated with susceptibility to bipolar disorder, without the need to engage in undue experimentation.

The Examiner concludes by stating at page 21 of the Office Action that "one cannot readily anticipate the identity or location of a particular gene, mutation or polymorphism that is associated with bipolar disorders." Applicants respectfully disagree with this conclusion and submit that based on the teaching of the D18S68-D18S979 region, one of skill in the art would anticipate that a coding region/gene, mutation, or polymorphism associated with bipolar disorder to be located within this newly identified region. Applicants submit that the knowledge of the D18S68-D18S979 region disclosed by Applicants, coupled with routine methods known in the art at the time of filing and described in the specification as filed, is more than adequate to allow one of ordinary skill in the art to use the methods as claimed with a reasonable expectation of success in finding a coding region associated with bipolar disorder.

In conclusion, Applicants submit that the claims as amended relate to methods for identifying at least one human gene that is associated with bipolar disorder. Claims 1 and 2 are not directed to specific genes or coding regions *per se* but rather relate to *methods* of identifying such genes or coding regions in the regions of chromosome 18 disposed between polymorphic markers D18S68 and D18S979 and between markers D18S60 and D18S61. The specification describes how the novel identification can be used to identify coding regions/genes or mutated or polymorphic variants within the newly identified region that are associated with a bipolar disorder. This novel identification of the region, the knowledge in the art, and the guidance provided in the specification are sufficient to allow one of ordinary skill in the art to practice the claimed methods throughout their scope. Applicants respectfully submit that on this basis, the standard for enablement has been met by the specification as filed.

Applicants submit that a full consideration of the amended claims in light of the factors set forth in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (CAFC 1988), supports the conclusion that no undue experimentation is required for enablement. Applicants therefore respectfully request the Examiner to withdraw the rejection of claims 1-5 under 35 U.S.C. §112 first paragraph.

Rejections under 35 U.S.C. §112

The Examiner rejected claims 1-5 under 35 U.S.C. §112, second paragraph as being indefinite. Claims 1 and 2 have been amended.

Applicants have amended the claims to remove the term "equivalent region" to clarify that the claimed methods compare a coding region in the DNA of an individual afflicted with bipolar disorder in a plurality of control individuals, which may include DNA from normal healthy individuals (see page 10, lines 25-35; page 10, lines 23-27) or the DNA in a YAC clone. Applicants submit that the amendment obviates the basis for the rejection.

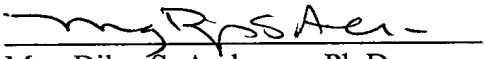
Accordingly, withdrawal of the rejection of claims 1-5 under 35 U.S.C. §112, second paragraph as being indefinite is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicants hereby request any necessary extension of time. If there is a fee occasioned by this response, including an extension fee that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Christine Van Broeckhoven et al., Applicants

By: 

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